45 Soft tissue sarcomas

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Cancers of soft tissue account for about 1% of all malignant neoplasms and for about 1% of all cancer deaths (Silverberg and Lubera, 1988). The tumors are derived from mesenchymal tissues other than bone and cartilage, and are by definition sarcomas. A diversity of cell types are seen, with tumors originating from muscle, fat, blood vessels, fibrous tissue, or other supporting tissue (Enzinger and Weiss, 1988a). Most soft tissue sarcomas (STS) are located in the space between the skin and visceral organs, where the tissue mass accounts for over 50% of the body weight, but they may also arise from the mesenchyme in any part of the body exclusive of bony structures.

DEMOGRAPHIC PATTERNS

Histopathology and Anatomic Distribution

The cell of origin and the site distribution of STS, by histologic type, are presented in Table 45–1.

Blood vessel sarcomas are currently the most commonly reported STS. This group includes Kaposi's sarcoma, hemangioendothelioma, and hemangiopericytoma. Kaposi's sarcoma, which has increased dramatically in recent years as a result of the acquired immunodeficiency syndrome (AIDS) epidemic, is characterized by spindle cells and vascular channels and slits (Safai, 1987). Although the precise cell of origin is uncertain, it is most likely the endothelial cell (Werner et al, 1989). Historically, the tumor was rare in Western countries, occurred mainly in men of Italian or Jewish background, and had an indolent clinical course. The incidence rose progressively with advancing age, with 70% to 90% of cases occurring in men, usually arising on the legs (Templeton, 1973). The classical form of Kaposi's sarcoma is uncommon in African Americans, but accounts for about 5% to 12% of all cancer in some African countries. In the 1980s, however, Kaposi's sarcoma was found increasingly in young and middle-aged men in association with AIDS (Biggar et al, 1984). These epidemic cases typically have a more aggressive clinical course than the classical or endemic form of Kaposi's sarcoma (Safai, 1987).

Hemangioendotheliomas are characterized by atypical endothelial cells lining vascular channels with anastomosing lumens (Stout, 1943). In children, the male-to-female ratio is 0.8. Hepatic hemangioendotheliomas often develop in the first year of life and are associated with cutaneous hemangiomas (Chabalko and Fraumeni, 1975). Hemangiopericytomas are characterized by malignant round cells outside the basement membrane of endothelial lined vascular channels. The most common site is the lower extremity, followed by the pelvic fossa (Enzinger and Smith, 1976).

Fibrosarcomas, the next most commonly reported STS, are confounded by uncertainties and variations in pathologic classification. Two types are generally recognized. The adult form consists of cells ranging from fibroblasts to anaplastic spindle cells. The tumors occur mainly at 40 to 70 years of age, and may follow an aggressive course depending on the histologic grade (Pritchard et al, 1974). In the infantile form the cells are similar but less mature, with an onset usually under 2 years of age and with a better prognosis (Chung and Enzinger, 1976). Adult sarcomas occur mainly on the trunk, followed by the extremities; the infantile tumors occur most often on the extremities (Iwasaki and Enjoji, 1979). There is a male predominance at all ages.

Leiomyosarcomas are composed of a continuum of cells, from smooth muscle cells to anaplastic spindle cells (Yannopoulos and Stout, 1962). The incidence of leiomyosarcoma of the uterus, the most common site of origin, is highest in the third and fourth decades of life and declines thereafter (Fig. 45–1). The rates for uterine leiomyosarcomas are much higher among African Americans than whites (Harlow et al, 1986). The next most common site is the gastrointestinal tract, with a male predominance in both races. Only about 1% of tumors arising from the prostate, bladder, and gastrointestinal tract occur in children. Most leiomyosarco-

TABLE 45–1. *Cell of Origin and Site Distribution of Soft Tissue Sarcomas by Histologic Type*

Histology	*Malignant Cell*	*Major Sites*
Blood Vessel Sarcomas		
Kaposi's sarcoma	Endothelial cells, spindle cells, vascular channels, and vascular slits	Extremities
Hemangioendothelioma	Atypical endothelial cells lining vascular channels with anastomosing lumens	Head and neck, trunk, extremities, liver
Hemangiopericytoma	Ovoid or round cells outside the basement membrane with endothelial lined vascular channels	Lower extremity, pelvic fossa and retroperitoneum, head and neck
Fibrosarcoma		
Infantile	Neoplastic spindle cells to primitive mesenchymal cells	Extremities
Adult	Fibroblasts to anaplastic spindle cells	Trunk, extremities
Leiomyosarcoma	Smooth muscle cells to anaplastic spindle cells	Uterus, gastrointestinal tract
Liposarcoma	Lipoblasts, adult fat cells, embryonal fat cells	Lower extremity, upper extremity, trunk
Rhabdomyosarcoma		
Embryonal	Small embryonal rhabdomyoblasts	Head and neck, genitourinary tract
Pleiomorphic	Rhabdomyoblasts	Extremities, trunk, head and neck, genitourinary tract
Synovial sarcoma	Spindle cells and epithelioid cells without basement membrane	Extremities
Mesenchymoma	More than 2 neoplastic mesenchymal cell types, excluding fibroblasts	Extremities
Lymphangiosarcoma	Endothelium of proliferated lymphatics	Extremities

mas occur in visceral organs and are missed entirely by classifications that rely on site-oriented codes.

Liposarcomas are composed of adult or embryonal fat cells or lipoblasts (Pack and Pierson, 1954). There is a male predominance at all ages and about 1% to 3% of tumors occur in children. The most common sites are the legs, arms, and trunk, in that order.

Rhabdomyosarcomas consist of primitive striated muscle cells and are the most common childhood STS. As shown in Figure 45–1, there is a peak incidence under age 5 and a smaller peak at 15 to 19 years. Embryonal tumors prevail in childhood and adolescence (Mahour et al, 1967). In early childhood the tumors arise in the head and neck, and genitourinary tract, especially the testis and paratesticular tissue. The male-to-female ratio is 1.2 for head and neck tumors and 2.0 for genitourinary tumors (Miller and Dalager, 1974). In adults the risk increases with age and is greater in men than women; the major cell type is pleiomorphic rhabdomyosarcoma. Tumors tend to develop in the legs, followed by the arms, trunk, head and neck, and genitourinary tract (Keyhani and Booher, 1968).

Mortality

A special handicap to the study of STS has been the failure of the International Classification of Diseases to categorize these tumors in a meaningful way. The site-oriented code for "connective tissue cancers" excludes mesenchymal tumors arising in parenchymatous organs and does not distinguish between the heterogeneous cell types. Tabulations based on topography and histology lead to considerably different results (Lynge et al, 1987). Since most sources of mortality data rarely contain or code histologic type, the reported death rates underestimate the true mortality of STS, perhaps by as much as one-half. In the United States, mortality rates are higher among nonwhites than whites and among men than women (Table 45–2).

Incidence

Like mortality, incidence data are affected by the assignment of STS to sites other than connective tissue. Examination of data from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program reveals that approximately one-half of the cases deemed to be STS, based on histologic data, are attributed to sites other than "connective tissue." For some cell types, the percent assigned to sites other than connective tissue is even greater. For example, approximately two-thirds of Kaposi's sarcoma cases are designated as malignancies of the skin. Age-adjusted incidence rates for STS, based on all cases in the SEER

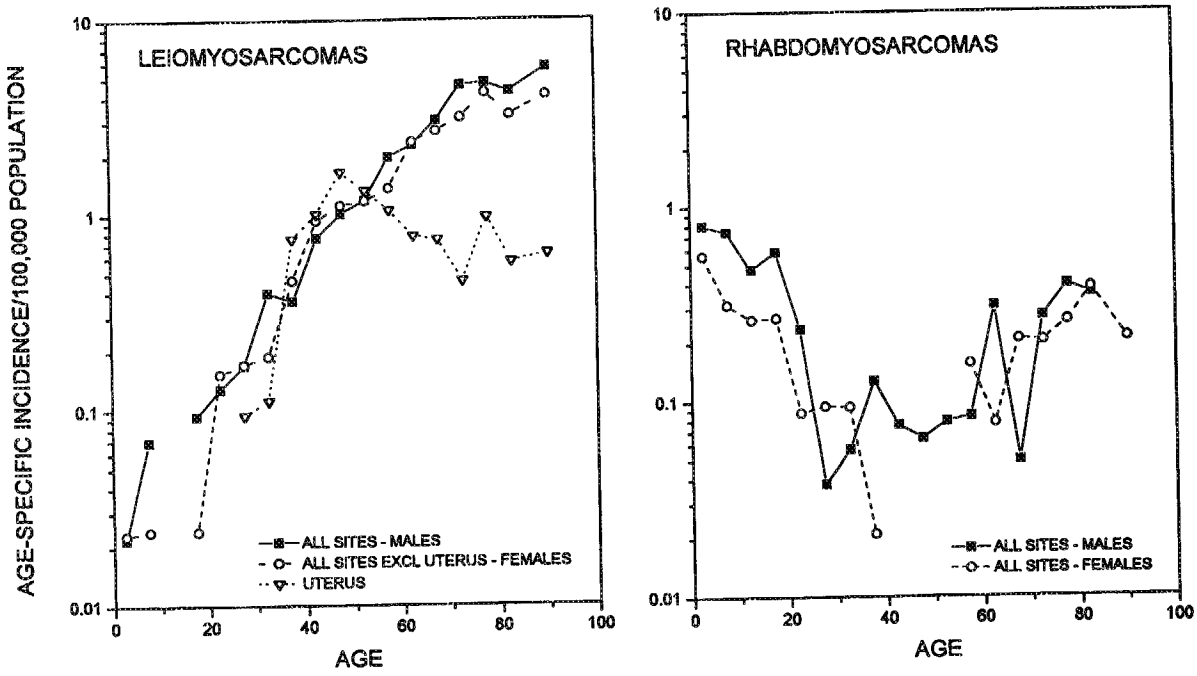

FIG. 45–1. Leiomyosarcomas and rhabdomyosarcomas in the 9 SEER areas, 1986–90.

program during 1986–1990, are presented in Table 45–3. The most common cell types are blood vessel sarcomas, fibrosarcoma, leiomyosarcoma, and liposarcoma, in that order. For all cell types combined and most individual cell types, there is a male excess. In particular, blood vessel sarcomas (primarily Kaposi's sarcoma) are over 20 times more common among white men than women. Leiomyosarcoma, on the other hand, is more common among women. The rates are generally higher among African Americans than whites, except for blood vessel sarcomas in men and liposarcoma in women. The largest racial difference is for leiomyosarcoma, particularly among women, which is consistent with incidence surveys from New York State (Polednak, 1986).

Since the SEER program covers about 10% of the U.S. population, it is usually possible to easily estimate the number of cancer cases expected to be diagnosed each year in the country. For STS, however, recent SEER data may overestimate the true national experience because SEER includes San Francisco, a geographic area with extremely high rates of AIDS and Kaposi's sarcoma.

Survival

The National Cancer Institute has evaluated the survival experience of cancer patients in the United States since 1950 (Axtell et al, 1976). As shown in Table 45–4, the 5-year relative survival rate was 36% for white patients with STS diagnosed during 1984–1989 (67% for localized and 34% for regional disease). The corresponding survival rate for African American patients was 38% (64% for localized and 46% for regional disease). The 5-year survival rates were highest for liposarcoma (whites: 73%; African Americans: 76%), and lowest for blood vessel sarcomas (whites: 13%; African Americans: 17%).

The survival rate for all STS combined has decreased

TABLE 45–2. *Average Annual Age-Adjusted Mortality Rates (per 100,000) for Connective Tissue Cancer in the United States by Pentad, Gender, and Race, 1950–1989**

	1950–54	*1955–59*	*1960–64*	*1965–69*	*1970–74*	*1975–79*	*1980–84*	*1985–89*
White men	0.49	0.60	0.71	0.81	0.85	0.85	1.19	1.23
White women	0.36	0.44	0.52	0.59	0.62	0.68	0.96	1.00
Nonwhite men	0.40	0.52	0.61	0.79	0.80	0.81	1.21	1.27
Nonwhite women	0.27	0.45	0.58	0.64	0.74	0.86	1.17	1.27

*Mortality rates are adjusted to the 1970 United States standard population.

over time due to the increased number of Kaposi's sarcoma cases, which have very low 5-year relative survival rates. There has been little to no change over time in the survival rates for the other histology types.

It has been suggested that the presence of estrogen receptors in leiomyosarcomas and liposarcomas might result in better survival among women than men (Chaudhuri et al, 1981). Among whites, there is little difference in 5-year relative survival by gender for leiomyosarcoma (women: 51%, men: 47%) or liposarcoma (women: 74%, men: 72%). Larger gender differences are observed among African Americans, however. African American women with leiomyosarcoma experience a 5-year relative survival rate of 43% while men have 17% survival. Similarly, the survival rate of African American women with liposarcoma (87%) is higher than for African American men (62%). Survival for women with fibrosarcoma is also better than for men (white women: 75%, white men: 69%, African American women: 78%, African American men: 62%).

The 5-year relative survival rates for all STS combined are significantly different for white men (27%) and women (56%), which is almost entirely attributable to the difference in survival rates for blood vessel sarcomas (e.g., Kaposi's sarcoma) (white men: 11%, white women: 53%). White men with rhabdomyosarcoma had better survival (56%) than women (48%). For most other types of STS, the survival is similar for both genders. Among African Americans, women also have higher survival than men for all types of STS combined (51% and 28%, respectively), primarily due to the large number and poor survival of male Kaposi's sarcoma cases (men: 14%, women: 55%).

Other factors thought to influence survival include histologic grade of malignancy, mitotic activity, presence of necrosis, tumor size, depth of tumors, bone and neurovascular structure infiltration, regional lymph node and distant metastases, anatomic location, adequacy of original surgery, local recurrence, altered expression of the retinoblastoma-susceptibility gene product, and socioeconomic status (Emrich et al, 1989; Tsujimoto et al, 1988; Mandard et al, 1989; Cance et al, 1990; El-Jabbour et al, 1990; Ciccone et al, 1991; Casson et al, 1992; El-Naggar and Garcia, 1992; Hashimoto et al, 1992; Pezzi et al, 1992).

TABLE 45–3. *Average Annual Age-Adjusted Incidence Rates (per 100,000) for Soft Tissue Sarcomas by Histologic Type, Race, and Gender**

Histology and Number of Cases	White		African American	
	Men	Women	Men	Women
Blood vessel sarcoma (4,843)	6.81	0.28	5.04	0.32
Fibrosarcoma (1,688)	1.54	1.09	1.88	1.48
Leiomyosarcoma (1,265)	0.80	1.10	1.22	2.01
Sarcoma, NOS (595)	0.53	0.44	0.72	0.50
Liposarcoma (573)	0.60	0.35	0.79	0.31
Rhabdomyosarcoma (259)	0.32	0.17	0.43	0.22
Stromal sarcoma (172)	0.02	0.23	0.03	0.34
Synovial sarcoma (120)	0.10	0.09	0.17	0.07
Meningiosarcoma (113)	0.07	0.09	0.20	0.08
Mesenchymoma (11)	0.01	<0.01	0.03	0.04
Lymphangiosarcoma (7)	<0.01	0.01	—	—
Others (661)	0.35	0.67	0.23	1.06
Total (10,307)	11.15	4.53	10.73	6.43

*From the Survival, Epidemiology, and End Results Program, 1986–1990, adjusted to the 1970 United States standard population. Case selection was based on histology codes.

Time Trends

Evaluation of time trends in the occurrence of STS is hindered by lack of long-existing databases with histology information (Lynge et al, 1987). Trends seen in site-oriented data may not accurately reflect changes in all

TABLE 45–4. *Five-Year Relative Survival Rates (%) for Patients with Soft Tissue Sarcoma Diagnosed in 1984–1989, by Histology, Race, and Stage*[a]

	All	Localized	Regional
White Patients (Number of Cases)			
All types (10,952)	36	67	34
Blood vessel sarcoma (5,025)	13	29	9
Fibrosarcoma (1,810)	71	82	74
Leiomyosarcoma (1,340)	50	70	38
Sarcoma, NOS (643)	35	65	37[b]
Liposarcoma (658)	73	82	72[b]
Rhabdomyosarcoma (274)	52	67[b]	61[b]
Stromal sarcoma (183)	69	83[b]	—[c]
Synovial sarcoma (138)	64[b]	77[b]	—[c]
Meningiosarcoma (117)	54[b]	—[c]	—[c]
African American Patients (Number of Cases)			
All types (1,263)	38	64	46[b]
Blood vessel sarcoma (408)	17	29[b]	20[b]
Fibrosarcoma (255)	70	77[b]	77[b]
Leiomyosarcoma (218)	36	54[b]	—[c]
Sarcoma, NOS (93)	21[b]	—[c]	—[c]
Liposarcoma (61)	76[b]	—[c]	—[c]
Rhabdomyosarcoma (46)	44[b]	—[c]	—[c]

[a]From the Survival, Epidemiology, and End Results Program. Case selection was based on histology codes, not site.
[b]Standard error between 5% and 10%.
[c]Number of cases too small to yield reliable rates; standard error greater than 10%.

TABLE 45–5. *Number of Cases and Average Annual Age-Adjusted Incidence Rates (per 100,000) for Kaposi's Sarcomas among Men by Calendar Period, Geographic Area, and Race*[a]

Race and Geographic Area	1975–1979		1980–1984		1985–1989	
	Count	Rate	Count	Rate	Count	Rate
White men						
9 SEER areas[b]	115	0.30	699	1.36	3,607	6.10
San Francisco	25	0.44	491	5.86	2,490	26.96
African American men						
9 SEER areas[b]	6	0.21	45	0.85	291	4.27
San Francisco	4	0.61	28	2.55	192	15.05

[a]From the Survival, Epidemiology, and End Results Program, 1975–1989, adjusted to the 1970 United States standard population.
[b]The nine Survival, Epidemiology, and End Results Program areas are the state of Connecticut; the Detroit, Michigan metropolitan area; the state of Iowa; the Atlanta, Georgia metropolitan area; the state of New Mexico; the state of Utah; the Seattle–Puget Sound, Washington area; the San Francisco–Oakland, California area; and the state of Hawaii.

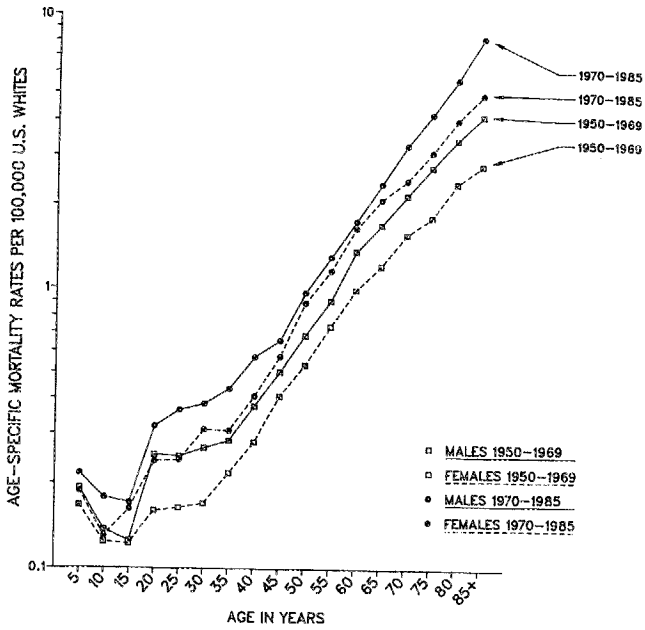

FIG. 45–2. Age-specific mortality rates per 100,000 for connective tissue cancers in the white population of the United States, by gender and calendar period, 1950–1969 and 1970–1985.

STS, because of the variable assignment of certain morphologic types to sites other than connective tissue. For example, in the SEER data, approximately two-thirds of cases of Kaposi's sarcoma, which rapidly increased as a result of the AIDS epidemic (Table 45–5), are assigned to the skin, whereas about one-half of all STS combined are assigned to sites other than connective tissue. Therefore, it is likely that reliance upon site-oriented data dampens observed trends for STS. In addition, large increases of Kaposi's sarcoma in high-risk areas, such as San Francisco, may be diluted in national statistics (Biggar et al, 1985).

Despite these limitations, upward trends in STS can be observed in both incidence and mortality statistics. Using data from the Connecticut Tumor Registry covering the years 1935–1989, an upward trend in incidence is seen for both genders, with a greater increase among men (Table 45–6). The increase in Kaposi's sarcoma peaked in the later 1980s, with declines in 1989 and 1990 (Ries et al, 1993). Based on HIV infection patterns, the Kaposi's sarcoma rates are expected to decline throughout the 1990s.

An upward trend for STS is seen in U.S. mortality statistics during 1950–1989, with the rate of increase being greater in nonwhites than whites (Table 45–2). Among men, the death rates were consistently higher in whites than nonwhites until the two most recent time periods, 1980–1984 and 1985–1989. Among women, the rates were higher in nonwhites starting in 1955–1959. As shown in Figure 45–2, the mortality rates among whites for 1970–1985 exceeded those for 1950–1969 in both genders. The increase affected all age groups. Similar increases in incidence and mortality in both genders have been reported in Canada (Ayiomamitis, 1988). Although the reported incidence and mortality rates have risen in a manner suggesting environmental influences, it is not possible to exclude the role of diagnostic and reporting practices. Because of the inherent problems in classifying STS, one cannot evaluate international variation or other geographic patterns in a meaningful way.

TABLE 45–6. *Average Annual Age-Adjusted Incidence Rates (per 100,000) for Connective Tissue Cancer in Connecticut by Calendar Period and Gender, 1935–1989**

	1935–39	1940–44	1945–49	1950–54	1955–59	1960–64	1965–69	1970–74	1975–79	1980–84	1985–89
Men	1.6	1.8	1.9	2.0	2.4	3.1	2.8	2.5	2.7	2.8	2.6
Women	1.5	1.7	1.4	1.7	1.8	2.0	1.7	1.7	1.5	2.1	1.6

*Incidence rates are adjusted to the 1970 United States standard population. Case selection was based on ICDO site code 171 only, not histology. STS of the heart are excluded.

ENVIRONMENTAL FACTORS

Radiation

A small fraction of STS is induced by external radiation therapy for various benign disorders and malignant tumors. In a study of multiple primary cancers in Connecticut, elevated risks of STS were observed in women who received radiation therapy for cancers of the breast and ovary. After at least ten years of follow-up, the risks for STS were elevated almost 8- and 25-fold, respectively, in the irradiated women (Harvey and Brinton, 1985; Curtis et al, 1985). In other tumor registry and cohort studies, significant increases in connective tissue tumors were reported following cancers of the breast, ovary, and testes and non-Hodgkin's lymphoma, while nonsignificantly elevated risks were noted following Hodgkin's disease (Taghian et al, 1991; Kaldor et al, 1987; Greene and Wilson, 1985). However, in hospital-based cohort studies of both children and adults treated for Hodgkin's disease, 40- and 15-fold increased risks of STS, respectively, were found (Tucker et al, 1984, 1988). In these two studies, all patients developing STS had received radiation to the anatomic site of the sarcoma.

The risk of uterine sarcoma is increased among women irradiated for cancer of the cervix (Czesnin and Wronkowski, 1978). A very high risk of radiogenic sarcoma with short latent periods (4 to 6 years) has been described in the orbital field of children treated for bilateral or familial retinoblastoma (Strong, 1977) and also in family members prone to sarcomas as part of Li-Fraumeni syndrome (Li et al, 1988).

In a series of 53 patients submitted to the Armed Forces Institute of Pathology, the latent period for post-irradiation STS varied from 2 to 40 years, with a mean of 10 years and a median of 8 years (Laskin et al, 1988). Other case series have similar range and mean latent periods (Kim et al, 1978; Davidson et al, 1986; Taghian et al, 1991; Mark et al, 1993). Nearly all cell types of STS have been described following radiation, the most common being malignant fibrous histiocytoma (Davidson et al, 1986; Laskin et al, 1988). Sarcomas secondary to radiation are usually diagnosed at a more advanced stage with higher grade and poorer prognosis than other sarcomas (Davidson et al, 1986; Robinson et al, 1988).

Few studies have assessed the risk of sarcoma according to the actual radiation dose delivered to the site of the sarcoma. In a study of STS following treatment for childhood cancer, 60% of the sarcomas arose within the field of radiation. Individual dosimetry to the site of the second sarcomas was determined. The risk of sarcoma was related to the total radiation dose to the site, with a greater than 50-fold excess in patients receiving over 50 Gy (Tucker MA, personal communication). It has been suggested that the level of risk of second tumors may be lower in patients treated with megavoltage than in those treated with orthovoltage (Potish et al, 1985). Total radiation dose, however, may be more important than the modality by which the radiation is delivered.

Thorotrast (colloidal thorium dioxide) is an alpha-emitting radioisotope once used for radiographic delineation of blood vessels. Its use was abandoned around 1955 when it produced several forms of cancer, most notably hepatic angiosarcomas (Locker et al, 1979; Van Kaick et al, 1983; Kato and Kido, 1987; Mays, 1988). The cumulative risk of liver cancers (angiosarcomas and carcinomas) is related to the dose rate to the liver tissue, reaching 30% at 40 years in the group receiving over 20 ml (approximately 30 rad/year) (Van Kaick et al, 1983). In the United States, the number of Thorotrast-induced angiosarcomas increased in the 1970s, resulting from the cumulative effects of low-dose procedures and prolonged latent periods (Falk et al, 1979a). Sarcomas of various types have also developed on the edge of Thorotrast deposits and granulomas, usually at injection sites (da Motta et al, 1979; Van Kaick et al, 1983). Other radioactive materials may induce sarcomas at or near sites of deposition, as suggested by a report of laryngeal sarcoma arising eight years after treatment of thyrotoxicosis by ^{125}iodine, which gives a higher extra-thyroidal dose than ^{131}iodine (McKillop et al, 1978).

In one study of low-frequency electromagnetic fields and childhood cancer, a nonsignificant association was observed between STS and measured magnetic fields in houses under low power use (Savitz et al, 1988). However, risk was lower for magnetic fields under high power use conditions. Excess incidence of STS was also observed in a cohort study of male Norwegian electrical workers potentially exposed to electromagnetic fields (Tynes et al, 1992). The authors noted that immunosuppression is a known etiologic factor for STS and that exposure to electromagnetic fields can alter the circadian cycle of pineal melatonin and affect immune function in animals.

Occupational Exposures

In Sweden, clinical observations (Hardell, 1977) prompted a case-control study that related STS to herbicide exposures (Hardell and Sandstrom, 1979). Among 52 patients with STS, a 6-fold increased risk was associated with occupational exposure to phenoxyacetic acids or chlorophenols. Because of the magnitude of the reported risk and the widespread potential for exposure, numerous studies were then conducted around the world. Results from these investigations, which have employed both case-control and cohort design and have focused on several exposure scenarios, have been inconsistent. Associations between STS and phenoxyacetic

acid herbicides and chlorophenols used primarily in agriculture and forestry were observed among men in four additional case-control studies in Sweden (Eriksson et al, 1981; Hardell and Eriksson, 1988; Eriksson et al, 1990; Wingren et al, 1990) and among women employed as rice weeders in Italy (Vineis et al, 1987). In addition, farmers were reported at excess risk for STS in England and Wales (Balarajan and Acheson, 1984). However, several studies, some with detailed exposure histories, have not shown any excess risk (Milham, 1982; Smith et al, 1982, 1983, 1984; Gallagher and Threlfall, 1984; Hoar et al, 1986; Wiklund and Holm, 1986; Woods et al, 1987; Wiklund et al, 1988; Serraino et al, 1992).

There have been several clinical surveys and cohort studies of manufacturing workers exposed to phenoxyacetic acid herbicides, chlorophenols, and their contaminants, such as 2,3,7,8-tetrachlorodibenzo-para-dioxin (2,3,7,8-TCDD) (Honchar and Halperin, 1981; Johnson et al, 1981). There has also been a case report of STS in a hospital worker exposed to hexachlorophene, a polychlorinated biphenyl detergent, produced from 2,4,5-trichlorophenol and contaminated by 2,3,7,8-TCDD (Hardell, 1992). Excesses of STS were found among manufacturing workers presumably exposed to 2,3,7,8-TCDD in the manufacture of trichlorophenols (Zack and Suskind, 1980; Cook et al, 1980; Cook, 1981; Johnson et al, 1981; Fingerhut et al, 1991) and among workers whose exposure to 2,4-dichlorophenoxyacetic acid (2,4-D), 2 methyl-4-chlorophenoxy acid (MCPA), and other phenoxyacetic acids were unlikely to be contaminated by 2,3,7,8-TCDD (Lynge, 1985, 1987). Chlorophenols may be responsible for an excess of STS observed in a small cohort of Italian leather tannery workers (Seniori Costantino et al, 1989). A review of the cases in some of the American cohorts, however, failed to confirm the diagnosis of STS or the exposure status of many of the cases (Fingerhut et al, 1984). In addition, other studies of chemical workers producing higher chlorinated phenols (Sobel et al, 1986; Ott et al, 1987), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) (Ott et al, 1980), MCPA (Coggon et al, 1986) and 2,4-D (Bond et al, 1988) did not detect excess STS.

Persons living in the vicinity of an Italian factory that accidentally released 2,3,7,8-TCDD into the environment were found to have a higher incidence rate of STS than residents in adjacent areas unaffected by the accident and in other parts of Italy (Puntoni et al, 1986; Bertazzi et al, 1989).

Excesses of STS have also been observed in several proportional mortality studies and clinical surveys of Vietnam veterans (Sarma and Jacobs, 1982; Anderson et al, 1986; Holmes et al, 1986; Kogan and Clapp, 1988), some of whom were exposed to Agent Orange, an herbicide mixture of 50% 2,4,5-T and 50% 2,4-D. However, other proportional mortality studies and several case-control studies have not observed any significant increases in STS risk for Vietnam veterans (Greenwald et al, 1984; Lawrence et al, 1985; Kang et al, 1986, 1987; Breslin et al, 1988; Goun and Kuller, 1988; Selected Cancers Cooperative Study Group, 1990b), including the Project Ranch Hand members who were directly involved with spraying Agent Orange (Lathrop et al, 1984). Verification of exposure has been extremely difficult in the veteran studies (Booth, 1987) and complex indices of exposure based on proximity to herbicide spraying in Vietnam have shown no meaningful correlation with 2,3,7,8-TCDD serum levels (Stellman and Stellman, 1986; Centers for Disease Control, 1989; Selected Cancers Cooperative Study Group, 1990a).

The reasons for the inconsistent results from studies of populations exposed to phenoxy herbicides or their contaminants are not known. Possible explanations include lack of comparable type and extent of exposure, differences in relevant contaminants, varying definitions of sarcomas under study, underascertainment of cases, recall bias, lack of sufficient latency, inherent susceptibility of study populations (e.g., Scandinavians), and chance (Blair and Zahm, 1990; Coggon and Acheson, 1982; Hardell and Axelson, 1982; Constable et al, 1987; Woods et al, 1987; Bond et al, 1989). To resolve these issues, improvements in exposure assessment and other study design features are needed.

The mechanism for an association between STS and phenoxy herbicides has been the subject of debate, especially for the herbicides not known to be contaminated by 2,3,7,8-TCDD. Immunosuppression, peroxisome proliferation, genotoxicity as evidenced by increased rates of sister chromatid exchanges, or inhibition of gap-junctional intercellular communication may play a role (Blair et al, 1990; Vineis and Zahm, 1988; Jennings et al, 1988; Tucker et al, 1986; Turkula and Jalal, 1985; Vainio et al, 1982; Korte and Jalal, 1982).

STS has also been associated with exposure to insecticides used on animals prior to the mid-1950s, in particular chlorinated hydrocarbon insecticides (Zahm et al, 1988). The excess risk appeared to be primarily for fibrous and myomatous sarcomas. Inorganic arsenical insecticides are a well-established cause of angiosarcomas of the liver (Popper et al, 1978).

Angiosarcomas of the liver are also caused by vinyl chloride exposures during the manufacturing of polyvinyl chloride plastics (Popper et al, 1978). A fibrotic precursor stage in the liver has been identified among individuals exposed to vinyl chloride, inorganic arsenic compounds, and Thorotrast. A survey of deaths from hepatic angiosarcoma in the United States during 1964–1974 recorded 168 cases, of which 37 (22%) were associated with vinyl chloride, Thorotrast, or inorganic arsenic (Falk et al, 1979b).

Two New Zealand case-control studies of cancer and

occupation found an association between STS and employment in an abattoir (Pearce et al, 1988). Abattoir workers may be exposed to plastics used to wrap meat (e.g., polyvinyl chloride), zoonotic oncogenic viruses, and various chemicals, including 2,4,6-trichlorophenol, which is used in the treatment of pelts.

An increased risk of STS observed among New Zealand forestry workers seemed related not to phenoxy herbicides, but possibly to the use of chain saws or other equipment (Reif et al, 1989). In addition, workers exposed to formaldehyde had excess mortality from cancers of the connective tissue in one study (Stayner et al, 1988), but not in others (Acheson et al, 1984; Blair et al, 1986).

Medicinal Agents

Angiosarcomas of the liver have been associated with inorganic arsenical medications (Fowler's solution) (Falk et al, 1981; Kasper et al, 1984) and with androgenic-anabolic steroids (Falk et al, 1979b), and possibly with estrogenic compounds (Ham et al, 1980).

Although an increased risk of STS following cancer chemotherapy is not well established, there is suggestive evidence for a relation to bone sarcomas and STS (Halperin et al, 1984; Tucker et al, 1987). Most treatment-related sarcomas are considered radiogenic whether or not chemotherapy is used (Laskin et al, 1988; Halperin et al, 1984; Tucker et al, 1988); but an excess risk of STS was reported after chemotherapy when used alone for Hodgkin's disease (Halperin et al, 1984). In a recent case-control study of second childhood cancers, the risk of STS was approximately 2-fold higher among patients receiving both radiation and alkylating agent chemotherapy than in subjects receiving only radiation (Tucker MA, personal communication). Doxorubicin has induced rhabdomyosarcoma following isolated limb perfusions in rats and the effect appeared to be dose dependent (Van't Hoff et al, 1986), but no data exist for humans. Further studies are needed to clarify whether alkylating agents or anthracyclines contribute to treatment-related sarcomas.

Various forms of STS, including Kaposi's sarcoma, have developed excessively after the use of immunosuppressive drugs, especially for renal transplantation, but also for other conditions (Kinlen et al, 1979). In addition, a survey of Kaposi's sarcoma in Norway over a 5-year period revealed that 6 of the 41 patients (15%) had taken immunosuppressive drugs for conditions other than cancer or transplants, while none of 242 control patients with basal-cell skin carcinomas used these drugs (Klepp et al, 1978).

In several case reports, sarcomas have arisen at the sites of previous iron-dextran injections (McIllmurray and Langman, 1978; Weinbren et al, 1978). Although these preparations have induced sarcomas in laboratory animals, the risk in man appears to be extremely small. Also, certain aluminum compounds, used as adjuvants in vaccines and allergenic extracts, have induced injection-site sarcomas in mice. An analysis of incidence trends in Connecticut, however, has revealed no increase in STS of the upper arms since 1963, when alum-adsorbed allergenic extracts were introduced (Jekel et al, 1978).

A number of chemicals have induced sarcomas in laboratory animals after subcutaneous or intramuscular injections. Although the significance of injection-site sarcomas has been debated, it is noteworthy that many of these compounds are also carcinogenic when tested experimentally by other routes (Boyland, 1980).

Parental use of the illegal drugs marijuana and cocaine has been linked to rhabdomyosarcoma in children (Grufferman et al, 1993). Use during the year preceding the child's birth was associated with a 2-fold to 5-fold increase in risk.

Viruses

More than a decade ago, a viral etiology of endemic Kaposi's sarcoma was hypothesized for several reasons. The geographic distribution in Africa resembled that of Burkitt's lymphoma; virus particles were identified in cell lines from African cases, which were later identified as cytomegalovirus (CMV); and serologic studies linked CMV to Kaposi's sarcoma in African, European, and North American cases (Giraldo et al, 1980; Giraldo et al, 1989; Safai, 1987). Studies of endemic African Kaposi's sarcoma have revealed no underlying immunodeficiency state (Kestens et al, 1985).

With the recognition of Kaposi's sarcoma in association with acquired immunodeficiency syndrome (AIDS), interest in the potential viral etiology of this tumor has intensified. Epidemic Kaposi's sarcoma is a more aggressive disease and tends to arise in younger individuals than the endemic variety (Safai, 1987). Relatively early in the AIDS outbreak, it was recognized that Kaposi's sarcoma was much more frequent in homosexuals with AIDS than in other risk groups, such as intravenous drug users, hemophiliacs, or transfusion recipients (Safai, 1987). The epidemiologic features of epidemic Kaposi's sarcoma suggest a sexually transmissable agent (Giraldo et al, 1989; Beral et al, 1992), particularly through anal intercourse with homosexual or bisexual men with AIDS. There is also some evidence that the incidence of Kaposi's sarcoma among homosexuals with AIDS has decreased somewhat in recent years (Des Jarlais et al, 1987), perhaps due to changing sexual practices. Although extensive laboratory investigations have attempted to isolate viruses from epidemic and endemic Kaposi's sarcoma, none have been successful to date. Efforts to identify viral sequences have yielded inconsistent results (Roth et al, 1988; Wer-

ner et al, 1989; Van Den Berg et al, 1989; Huang et al, 1992; Nickoloff et al, 1992; Biggar et al, 1992; Chang et al, 1994; Collandre et al, 1995; Boshoff et al, 1995), but epidemiologic and molecular studies are continuing to search for a viral agent that may be transmitted by fecal-oral contact or blood products.

Although a viral etiology of other sarcomas has been hypothesized because of animal models, the epidemiologic data are very limited. One case-control study from Italy found slightly elevated risks of STS associated with a history of childhood chicken pox or mumps (Serraino et al, 1991). There was also an increased risk of sarcoma associated with a history of herpes zoster, particularly in the three years prior to diagnosis. This association may be due to an underlying immune deficiency, which predisposes both to infection and to the development of sarcoma.

Other Environmental Factors

It has been suggested that trauma may increase the risk of STS, but the available evidence suggests that local injury only calls attention to a preexisting tumor and perhaps accelerates its growth. Sarcomas have been reported at the sites of surgical scars (Ott, 1970), burn scars (Enzinger and Weiss, 1988b), and in the soft tissue near metals used for bone fracture fixation (Dube and Fisher, 1972; Lee et al, 1984), and more recently at the site of total hip arthroplasty (Swann, 1984; Ryu et al, 1987). Although such occurrences appear to be rare, clinical reports of sarcomas at the site of bone implants have raised concern (Rock and Unni, 1990). To date, epidemiologic studies have revealed no excess risk of STS or bone cancer after hip replacement with metal implants (Nyren et al, 1995).

The risk of breast sarcomas among women with silicone breast implants is under investigation (Brinton, 1993), although examination of SEER incidence rates of breast sarcomas shows little or no change over time (May and Stroup, 1991; Engel and Lamm, 1992). Given the low incidence of the disease and the low prevalence of the exposure, however, examination of incidence rates in the general population is limited in its ability to assess an association.

There has been one case-control study relating STS to the use of smokeless tobacco (Zahm et al, 1989). The risk associated with chewing tobacco or snuff was more pronounced for sarcomas of the upper gastrointestinal tract, the lung and pleura, and the head, neck, and face region than for lower regions of the body. Lip sarcomas and other tumors have been reported in rats exposed to snuff, possibly a consequence of N-nitrosamines (Johansson et al, 1989). A cohort study of U.S. veterans, however, showed only a nonsignificant 40% excess of mortality from STS among smokeless tobacco users with no striking risk patterns by characteristics of use, although frequent users had a slightly higher risk than infrequent users (Zahm et al, 1992).

Cigarette smoking has not been linked with STS (Hardell and Sandstrom, 1979; Gebauer, 1982; Kang et al, 1987; Vineis et al, 1987; Woods et al, 1987; Hardell and Eriksson, 1988; Zahm et al, 1989; Serraino et al, 1991). However, a study of rhabdomyosarcoma among children revealed an excess risk associated with paternal (but not maternal) smoking (Grufferman et al, 1982). An interaction between cigarette smoking and occupational exposure to 2,3,7,8-TCDD in the development of STS has been suggested among heavily exposed workers (Cook, 1981).

Information on the role of dietary factors in STS is very scarce. One case-control study suggested an increased risk associated with a high intake of dairy products and oil (i.e., mostly seed oil) and a decreased risk associated with whole-grain bread and pasta (Serraino et al, 1991). In another study, rhabdomyosarcoma in childhood was related to diets that included organ meats (e.g., liver, brain, and tongue) (Grufferman et al, 1982).

HOST FACTORS

Precursor Lesions

Sarcomas generally have benign counterparts (e.g., lipomas), which are at least five times as common, but nearly all sarcomas appear to be malignant from the start and do not evolve from precursor tumors (Morton, 1973). Although malignant change of benign tumors is a rare event, transformation can be promoted by ionizing radiation as used in therapy of angiomas (King et al, 1979).

Genetic Factors

Li-Fraumeni syndrome was initially recognized in four families with an autosomal dominant pattern of STS, breast cancer, and other tumors in children and young adults (Li and Fraumeni, 1969). Subsequent experience with nearly 100 families with Li-Fraumeni syndrome have expanded the tumor phenotype to encompass osteosarcoma, brain tumor, leukemia, adrenocortical carcinoma, and germ cell tumors (Blattner et al, 1979; Strong et al, 1987; Li et al, 1988; Hartley et al, 1989). Another feature is the tendency for multiple primary tumors to occur in individual family members, including a susceptibility to second cancers, notably STS, arising in the radiotherapy field. Epidemiologic studies have excluded the role of chance and selection or referral bias as an explanation for the familial aggregations. Pro-

spective studies of Li-Fraumeni kindreds have revealed continued expression of the component tumors, with the greatest risk among those under age 20 (Li and Fraumeni, 1982; Garber et al, 1991). Other surveys have shown excesses of breast cancer in the mothers of patients with STS, osteosarcoma, or chondrosarcoma (Birch et al, 1990; Hartley et al, 1986). Furthermore, segregation analysis of several families of children with STS have confirmed an autosomal dominant pattern of the various tumors characteristic of Li-Fraumeni syndrome (Williams and Strong, 1985). In affected families, the recent discovery of germ line mutations of the tumor-suppressor gene, p53, which is located on chromosome 17p13, has important implications to the origins and prevention of STS as well as other component tumors of the syndrome (Malkin et al, 1990). Recommendations for predictive p53 testing of at-risk individuals in Li-Fraumeni families should be useful in strategies for testing other cancer susceptibility genes that are discovered (Li et al, 1992).

Along with osteosarcoma, STS occurs more often than expected in survivors of the hereditary form of retinoblastoma (Sanders et al, 1989). The mesenchymal tumors often arise in the lower extremities, but also develop excessively in the irradiated field around the orbit. Mutations of the retinoblastoma gene (Rb-1), which has been mapped to chromosome 13q14, appear to account for the heritable retinoblastomas as well as subsequent sarcomas (Hansen et al, 1985). Rb-1, a tumor-suppressor gene, is altered also in the tumor tissue of some sporadic sarcomas (Cance et al, 1990), while specific morphologic subtypes show a number of genetic defects, including chromosomal translocations, point mutations, and allele loss (Knight, 1990; Li, 1988). Although Rb-1 appears to be implicated in adult sarcomas, one study of childhood rhabdomyosarcoma did not observe any structural or functional abnormalities in Rb-1 (De Chiara et al, 1993).

Another dominantly inherited trait predisposing to STS is neurofibromatosis type 1. Neurogenic sarcomas (e.g., neurofibrosarcoma) occur with excess frequency, especially in adults (Hope and Mulvihill, 1981; Bader, 1987). In children, rhabdomyosarcomas arise excessively (McKeen et al, 1978), along with fibrosarcomas and liposarcomas. In Gardner's syndrome, familial polyposis occurs with a spectrum of mesenchymal lesions, including desmoid tumors, aggressive fibromatosis, and rarely fibrosarcoma.

In addition, clinical reports have linked the nevoid basal cell carcinoma syndrome to fibrosarcoma and rhabdomyosarcoma, tuberous sclerosis to rhabdomyosarcoma, and familial hydronephrosis to congenital renal sarcomas (Mulvihill, 1975). A familial syndrome of cutaneous and uterine leiomyomas, sometimes complicated by uterine leiomyosarcomas, has been described (Walker and Reed, 1973). Carney's triad is a syndrome of gastric leiomyosarcoma, pulmonary chondroma, and extra-adrenal paraganglioma, which has been reported in a series of young women (Margulies and Sheps, 1988). The tumors tend to be multicentric, but familial occurrences are yet to be seen. A few patients with genetic hemochromatosis have developed hepatic angiosarcomas (Sussman et al, 1974), although hepatocellular carcinoma occurs more often as a complication. An association between melanoma and STS has been reported recently, but the mechanism involved is unclear (Garber et al, 1990). The association may be due to the same mechanism as the newly described familial constellation of Ewing's sarcoma family of tumors, melanoma, brain cancer, and possibly stomach cancer (Novakovic et al, 1994).

Werner's syndrome (adult progeria) is a recessively inherited disorder featuring a shortened life span due to early atherosclerosis and cancer. Most common are sarcomas, perhaps related to the retarded growth of skin fibroblasts in vitro (Lutzner, 1977). Congenital multiple fibromatosis, which appears inherited in some cases, resembles low-grade fibrosarcoma, although the tumors regress and eventually disappear a few months after birth (Baird and Worth, 1976).

Immunologic Defects

An STS excess has been reported in patients receiving therapeutic immunosuppression for renal transplantation and other conditions, although the risks are not nearly as high as for non-Hodgkin's lymphoma (Hoover and Fraumeni, 1973; Kinlen et al, 1979). In the genetic immunodeficiency syndromes, there is also a predominance of lymphoid tumors and a suggestion that STS is overrepresented among the other tumors reported (Spector et al, 1978). Patients with chronic lymphocytic leukemia are also prone to STS, apparently as a result of the immunodeficiency state associated with this form of leukemia (Greene et al, 1978). Similarly, the immunodeficiency associated with non-Hodgkin's lymphoma and Hodgkin's disease may contribute to the excess risk of STS (Tucker et al, 1988; Halperin et al 1984; Greene and Wilson, 1985; Kaldor et al, 1987).

Kaposi's sarcoma is especially prominent among the posttransplant cases of STS (Harwood et al, 1979), and this tumor also develops excessively among patients with lymphoproliferative neoplasms (Safai et al, 1980) or autoimmune hemolytic anemia (Hammond et al, 1977). It is noteworthy that various immunodeficiency states, including AIDS and the use of immunosuppressive drugs, predispose to STS as well as lymphoma, so that intact immunosurveillance mechanisms may be important in controlling both kinds of tumors.

Other Host Factors

Lymphangiosarcomas may arise in the chronically edematous arms of women who have undergone radical mastectomy for breast cancer (Stewart-Treves syndrome). Several cases of lymphangiosarcoma have also been reported following long-standing lymphedema of a congenital or heritable nature (Dubin et al, 1974). Sarcomas have appeared as well in families with the lymphedema-distichiasis syndrome (Falls and Kerlesz, 1964). In addition, sarcomas have arisen at the site of chronic skin ulcers (Routh et al, 1985; Fletcher, 1987).

Childhood rhabdomyosarcoma has been linked in one study to maternal history of stillbirth with risk increasing with the number of prior stillbirths (Ghali et al, 1992). The data suggest that rhabdomyosarcoma and stillbirths may share a common risk factor that is either genetic or may involve in utero exposure to an exogenous or endogenous agent. Rhabdomyosarcoma also shows a rise in risk at puberty, with the peak for girls occurring about two years earlier than that for boys, coincident with differences in muscle growth patterns, suggesting that hormones may play a role (dos Santos Silva and Swerdlow, 1993).

PREVENTIVE MEASURES

The present state of knowledge of STS risk factors, although incomplete, has important implications for the detection and prevention of these tumors. Persons at high risk (e.g., as a result of radiation exposure, immunosuppression, or genetic susceptibility) need appropriate medical surveillance, including the judicious use of computed tomography or magnetic resonance imaging aimed at the early diagnosis and characterization of soft tissue tumors. Appropriate steps should be taken, of course, to reduce potentially hazardous exposures to ionizing radiation and certain chemicals, such as vinyl chloride, arsenic, and phenoxyacetic acid herbicides. Adherence to the recommendations to inhibit the transmission of the human immunodeficiency virus (Goedert, 1987) would decrease the risk of Kaposi's sarcoma associated with AIDS.

FUTURE RESEARCH

Epidemiologic progress in understanding STS has been hindered by uncertainties in the morphologic classification of this diverse group of neoplasms, and it is hoped that refinements in diagnostic criteria will strengthen the basis for further studies. The epidemiologic variation by cell type have suggested some degree of etiologic heterogeneity, although there is evidence that some risk factors are shared by different forms of STS.

Ionizing radiation at high doses is known to produce a variety of sarcomas, but accounts for only a small fraction of cases. Thorotrast, vinyl chloride, inorganic arsenic, and androgenic steroids can induce hepatic angiosarcomas, and recent studies have linked STS with occupational exposure to herbicides, mainly phenoxyacetic acids and chlorophenols. Further case-control studies of STS are obviously indicated, particularly in view of the climbing incidence and mortality rates for these tumors. More research is needed on the etiologic role of chemotherapy, immunosuppressive drugs, and orthopedic implants in sarcomas, while future studies on the effects of pesticides and other environmental exposures will require improved methods for assessing historical exposures. Research is also needed to pursue the suggested associations between STS and use of smokeless tobacco, exposure to electromagnetic radiation, and the possible role of nutritional factors.

The bimodal age curve for STS includes an initial peak in early childhood that has long suggested the role of prenatal factors. In Li-Fraumeni syndrome, the tendency for childhood sarcomas and other tumors to cluster in families has provided direction for molecular research to probe into genetic mechanisms of carcinogenesis, including the role of the tumor-suppressor gene, p53, in various forms of STS. Further work is needed on genetic-environment interactions, as illustrated by the excess of radiogenic sarcomas in Li-Fraumeni syndrome and in heritable retinoblastoma. The higher incidence of STS in African Americans than in whites may also reflect genetic determinants underlying the risk and biologic behavior of certain STS subtypes, although other risk factors need to be evaluated as well.

Recent evidence suggests that various states of immunosuppression, particularly T-cell abnormalities, predispose to STS, although the risks are not nearly as high as for lymphoproliferative neoplasms. Kaposi's sarcoma is conspicuous among the tumors complicating immunosuppression, most notably AIDS, and occurs excessively in patients with lymphoid neoplasms. These observations suggest common or related etiologies for lymphoma and STS, especially the Kaposi type. Further research into AIDS-associated tumors should clarify the role of oncogenic viruses, immune defects, growth factors, and other mechanisms of carcinogenesis. Based on recent progress, it seems likely that interdisciplinary approaches aimed at clarifying host and environmental determinants of STS will contribute more broadly to a better understanding of cancer biology, etiology, and prevention.

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